In paragraph five of the Office Action, claims 6, 7, 11, 15 and 19 are objected to as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim. By the amendments made at this time, the multiple claim dependency problem is obviated.

Additionally, Applicants also appreciate the indication with respect to the prior art rejections, in which a statement is set forth that the claims objected to are also believed to be subjected to anticipation and /or obviousness rejections. As will be apparent from the discussion of the prior art rejections herein below, Applicants submit that all claims should be in condition for allowance. All the claims objected to in paragraph 5, will be shown to be dependent upon an allowable claim, and of course, have also been amended to obviate the multiple claim dependency objection.

Before proceeding with a discussion of the prior art rejections, Applicants wish to first of all direct the Examiner's attention to the claim amendments.

Disregarding claims 17-18 withdrawn from consideration as directed to a non-elected invention, Applicants' claims prior to the present amendment consisted of claims 1-11 directed to photocured crosslinked-hyaluronic acid gels; method claims 12-14 directed to methods for preparing such gels; biomedical material claims 15 and 16; and biomedical material kit claims 19 and 20, the latter biomedical material and biomedical material kit claims including the photocured crosslinked-hyaluronic acid gels of Applicants' product claims.

Turning first to the photocured crosslinked-hyaluronic acid gel claims 1-11, the Examiner will note that prior to the present amendment, claims 1, 2, 3, 8, 9 and 10 were all independent claims. Out of those, the Examiner had indicated that claim 10 is allowed.

At this time, dependent claim 4 has been inserted into independent claim 1, while independent claims 2 and 3 have been amended to be dependent on amended claim 1. This of course resulted in the cancellation of claim 4. Additionally, claim 1 has been further amended to recite that the photocured crosslinked-hyaluronic acid hydrogels (the term "hydrogel" has now been consistently used throughout the claims) is injectable, which is an inherent characteristic of the amorphous product being claimed. Newly added product claim 21 is directed to the injectable feature of the product by specifying that it is capable of being pushed out of a container (of course, such a "container" can be a syringe or similar instrument).

An important characteristic of the product claimed by Applicants in claim 1, is that it is of an indefinite shape. This feature is set forth in the specification of the viscoelastic characteristics in the first part of the claim. See page 33, lines 2-13 of the present application. When the hydrogel of the present invention is used as an antiadhesive material, a balance of the viscosity and the elasticity is important. If G' exceeds 1500 or the tangent delta is less than 0.1, the gel become highly elastic gel, so-called hard and brittle gel, and it becomes difficult for the gel to be injected into an affected part. On the other hand, if G' is less than 50 or the tangent delta exceeds 0.8, the gel becomes highly viscous gel behaving like a solution, failing to provide desirable hardness, and a barrier effect required for antiadhesive effect is lost. Namely, the hydrogel of the present invention has the most suitable physicochemical properties (viscoelasticity) as an antiadhesive material. Also, since the hydrogel of the present invention has an indefinite form, it can have specific viscoelasticity.

In addition, generic claim 1 recites that the photoreactive crosslinking group is a cinnamic acid derivative containing a spacer and chemically links to a functional group of the

hyaluronic acid to form the photoreactive hyaluronic acid which is then crossed-linked in order to form a cyclobutane ring resulting in the network structure which contains the aqueous medium of the hydrogel.

Independent claims 8, 9 and 10 (10 having been allowed) also recite the viscoelastic characteristics of claim 1 providing the indefinite shape to the product, plus include the concept that the irradiation of the hydrogel containing the photoreactive hyaluronic acid is carried out in an aqueous medium solution, with a heat treatment after (claim 8) or prior (claim 9) to the irradiation. Allowed claim 10 contains two stages of heat treatment. The Examiner will note that claims 8 and 9, similar to allowed claim 10, because of the product by process limitations thereof concerning the use of the aqueous medium and heat treatment, do not recite a specific recitation of the chemical structure of the photoreactive crosslinking group as set forth in claim 1.

Turning to the method of preparation claims, originally only claim 12 was set forth in independent form . In claim 12, the hydrogel is formed by irradiation as an aqueous solution of the photoreactive hyaluronic acid derivative. Concentration is set forth. Allowable claim 14 has now be rewritten in independent form, leaving dependent claim 13 as the only dependent method claim. In dependent claim 13 a heat treatment is carried out before and/or after irradiation of the aqueous medium solution.

In paragraph 8 of the Office Action, claims 1-6, 9, 10, 12, 13 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over the Matsuda et al. EP '898.

The Examiner's position may be summarized in the context that the Examiner considers that the photocross linked-GAG of Matsuda EP '898 (hereinafter "Matsuda") is formed from the same reactants as Applicants' hydrogel and as a result, the film of Matsuda (the Examiner recognizes the film structure of Matsuda at page 6, line 16 of the Office Action) would inherently contain the viscoelastic characteristics of Applicants claim 1, that is, would contain the storage modulus (G^{I}), loss modulus (G^{II}) and tangent delta (G^{II}/G^{I}) numerical parameters, all as set forth in Applicants generic claim 1, as well as generic claims 8 and 9. This is not the case, as explained below.

Matsuda does not disclose the dynamic viscoelasticity described in the present invention. The importance of the viscoelasticity of the photocured crosslinked-hyaluronic hydrogel in the present invention is described at page 33, lines 2-13 in the present specification, and has been discussed earlier in this amendment. These properties provide the indefinite shape or amorphous characteristic ("amorphous" is used herein in the context of its common dictionary meaning of "having no definite form: shapless") of the hydrogel of the present invention (see page 34, lines 7-17). This amorphousness of the hydrogel of the present invention allows it to be injected through a needle, from a syringe or the like and provides its superior antiadhesive characteristics when used as a biomedical material. In contrast Matsuda is concerned with molded or casted materials, in particular films. This is apparent from the examples of Matsuda, such as example 11. Such a finite structure and shape such as a film cannot have the viscoelastic characteristics of Applicants' generic product claims, which are defining an indefinite amorphous shape.

In example 27 of Matsuda, a hydrogel is formed from the film absorbing water. Even so, the structure is a definite structure as a film, and that is what is used as a biomedical material, as shown at page 28, line 56, of Matsuda.

Consequently, the products of Matsuda do not have the specific viscoelasticity defined in the present invention, and therefore, the novelty of the present invention based on the viscoelasticity is not destroyed by the disclosure of Matsuda.

As a result of limitation of new claim 1, the gel of the present invention is limited to hydrogel containing an aqueous medium in a network structure formed by a cyclobutane ring formed by dimerizing the mutual photoreactive crosslinking groups (i.e., cinnamic acid derivative containing a spacer) of the photoreactive hyaluronic acid derivative by irradiation with ultraviolet rays, which is an injectable photocured crosslinked-hyaluronic acid hydrogel.

With the above in mind, Applicants now turn to a discussion of significant features of the present invention. These are discussed for the Examiner's reference.

The features of a photocured crosslinked-hyaluronic gel of the present invention are as follows and the like:

(1) the gel is a hydrogel having a specific viscoelasticity, such as a storage modulus, a loss modulus, and a tangent delta (claim 1);

(2) the hydrogel is obtained by irradiating with ultraviolet rays an aqueous medium solution containing a photoreactive hyaluronic acid derivative at a suitable concentration (e.g., 0.5 to 10 wt%) and by inducing a cross reaction in the solution (claim 12);

(3) the photoreactive hyaluronic acid derivative which is an intermediate compound of the gel of the present invention in which a photoreactive crosslinking group (i.e., cinnamic acid derivative) having a spacer is chemically linked to a functional group of the hyaluronic acid (claim 1);

(4) the mutual photoreactive crosslinking groups of the photoreactive hyaluronic acid derivative are dimerized by irradiation with ultraviolet rays to form a cyclobutane ring and to thereby form a network structure, and the hydrogel contains an aqueous medium in the network structure (claim 1);

preferably,

(5) the gel has a very high water absorption (2,000 to 15,000%) (claim 3);

(6) the photoreactive crosslinking group is introduced with such a low degree of substitution {DS (the ratio (%) of introduction of the photoreactive crosslinking group per constituent disaccharide unit of hyaluronic acid): 0.05 to 10%} per mole of a constituent disaccharide unit of hyaluronic acid (claim 7), and the crosslinking extent which is the product of the DS and the crosslinking ratio is as low as 0.01 to 0.5% (i.e., the crosslinking ratio is 0.001 to 10%) (claim 2); and

(7) the specific viscoelasticity of the hydrogel in the above item (1) is improved by a combination of the high water absorption in the above item (5), the low crosslinking extent in the above item (6), and the like.

Moreover, the hydrogel of the present invention whose physicochemical properties and the like are controlled in a proper range as described above shows the following superior effects

and the like when used as an antiadhesive material available to tissues or internal organs of animals:

(a) the hydrogel shows superior antiadhesive effects;

(b) the hydrogel can be injected into affected parts, i.e., it is easily handled because of its suitable dynamic viscoelasticity;

(c) the hydrogel exhibits high stickiness to tissues, and remains at affected parts for a period necessary for antiadhesion;

(d) the hydrogel has suitable biodegradability, i.e., it is metabolized and excreted after performing the effect of antiadhesion by remaining at affected parts for a necessary period;

(e) the hydrogel has safety, i.e., it maintains the intrinsic property of hyaluronic acid as a biomaterial because of the suitability of water absorption, the degree of substitution of the photoreactive crosslinking group and the crosslinking ratio, and the resulting crosslinking extent.

With respect to Applicants'claim 2, the Examiner has referred to the degree of substitution (DS) being between about 0.1 to 3.0 in Matsuda and submits that this reads on the limitation of claim 2.

However, Matsuda does not disclose or suggest the crosslinking extent defined in the present invention. Claim 2 does not define a DS, but a crosslinking extent. The crosslinking extent is described at page 26, lines 3-19 in the present specification. Specifically, the crosslinking extent is a product of a DS and a crosslinking ratio. The DS of 0.1 to 0.5 in Matsuda corresponds to 10 to 50% in terms of the crosslinking ratio defined in the present invention (see page 24, lines 14-25 in the present specification).

With an increase in the crosslinking ratio of the photocured crosslinked-hyaluronic acid gel (the ratio of cyclobutane ring formed by crosslinking the photoreactive hyaluronic acid derivative), the network structure of the gel becomes denser, and the nature of the gel as an elastic material increases. Therefore, in order to maintain the above preferable value of the viscoelasticity, the crosslinking extent which is the product of the DS and the crosslinking ratio is preferably adjusted to the range of from 0.01 to 0.5% per mole of a constituent disaccharide unit of hyaluronic acid, as claimed in claim 2.

One illustration of the marked difference between the hydrogel of the present invention having an indefinite shape and the form structure of Matsuda is the way in which swelling capacity is calculated.

In Matsuda, as described at page 18, lines 25-27, the swelling capacity is calculated as absorption weight by subtracting the dried film from the swollen film. Example 15 (Table 4) pointed out by the Examiner shows the values measured in such a manner. On the other hand, in the present invention, as described at page 48, lines 1-21, since the hydrogel of the present invention has an indefinite form and cannot be measured under swelling conditions, the water absorption is measured by a specific method in which a dried gel is put in a Blue Dextran ("B.D.") solution for absorbing water and the B.D. concentration in the B.D. solution is measured before and after the water absorption.

Furthermore, the Examiner asserts that Matsuda discloses swelling capacities that appear to read on the limitations of claim 3. However, the products in Examples 15 and 18 of Matsuda are films having a definite form and are obtained by irradiating light to a dried film in the same manner as in Examples 1 and 2 of Matsuda., which is a different form from the hydrogel of the

present invention having an indefinite form, and therefore, the Matsuda films do not have the viscoelasticity defined in the present invention, even if the water absorptions in Examples 15 and 18 of Matsuda partially overlap with those of the present invention.

Additionally, the products in Examples 15 and 18 of Matsuda are obtained by using a thymine derivative. On the other hand, the hydrogel of the present invention is obtained by using a cinnamic acid derivative containing a spacer as a result of amended claim 1, instead of the thymine derivative. Accordingly, it is apparent that the products in Examples 15 and 18 of Matsuda are quite different from the hydrogel of the present invention. Of course, since claim 3 is now a dependent claim, it also is allowable for all of the reasons why claim 1 is allowable.

From this difference in the measurement of the water absorption, one of ordinary skill in the art would easily understand that the hydrogel of the present invention having an indefinite form is quite different in properties from the film described in Matsuda.

With respect to Applicants' claims 8, 9, and 11, the Examiner submits at page 6, lines 8-14 that the UV irradiation range is that of claim 8 and example 12 of Matsuda as teaching crosslinking reaction under heating verses photo initiation anticipates claim 9.

The heating treatment of the present invention is different from Matsuda. For example, the drying in Example 27 of Matsuda was carried out to remove ethanol. On the other hand, the heating treatment in the present invention is carried out for improving the viscoelasticity requirements and sterilizing the produced medical devices or medicines (see the first full paragraph at page 29 in the present specification). Accordingly, it is apparent that the drying of Matsuda is not carried out for the heating treatment disclosed in the present invention, but for simply drying.

As noted, the Examiner asserts that in Example 12, Matsuda teaches that the crosslinking reaction can be under heating vs. photo initiation, and this anticipates claim 9. However, Example 12 of Matsuda only discloses that in the synthesis of the photocurable GAG (HA-Thym-1), the reaction was carried out at 90°C. Therefore, the reaction is different from claim 9 reciting heating treatment of the photoreactive hyaluronic film which has been already synthesized.

Consequently, Matsuda does not disclose or suggest the heating treatment in the present invention, and therefore the novelty of the present invention based on the heating treatment cannot be destroyed by the disclosure of Matsuda.

Furthermore, in Matsuda, irradiation is carried out to a dried film. On the other hand, in the present invention, claims 8 and 9 are limited to irradiation in an aqueous medium solution. Therefore, the present invention in which the irradiation is carried out in an aqueous medium solution can be distinguished in a patentable sense under 35 U.S.C. § 103 from Matsuda disclosing the irradiation to the dried film. Claims 8, 9, and 11 are novel and unobvious over Matsuda.

Next, Applicants turn to method claims 12 and 13. The Examiner is requested to carefully note that in these claims, the irradiation is carried out in an aqueous medium solution and this is nowhere taught or suggested by Matsuda.

As discussed above, in Matsuda, irradiation is carried out to a dried film. On the other hand, in the present invention, irradiation is carried out in an aqueous medium solution. Therefore, the present invention in which the irradiation is carried out in an aqueous medium

solution can be distinguished in a patentable sense from Matsuda disclosing the irradiation to the dried film.

Furthermore, the Examiner asserts that in Example 1, Matsuda teaches that the solution of the photocurable GAG was heat sterilized before photocuring with the photoreactive group, and this anticipates claim 13. However, Example 1 of Matsuda only discloses that a film was formed by drying a DMF solution of photocurable GAG (HA-Cin-3) on a slide glass at 40°C, and sterilization cannot be conducted by this step. Additionally, since the final product in Matsuda Example 1 is a film, the step has no influence on the viscoelasity of the photocured crosslinked-GAG.

In summary, with respect to paragraph 8 of the Office Action, the present inventors found that the hydrogel of the injectable photocured crosslinked-hyaluronic acid having the above range of the viscoelasticity, and optionally the crosslinking extent and the very high water absorption, is injectable into an affected part of tissues and organs of living bodies so as to prevent adhesions and that the hydrogel has the superior effects as described above, and have thereby achieved the present invention. Such knowledge or information is neither disclosed nor suggested in Matsuda.

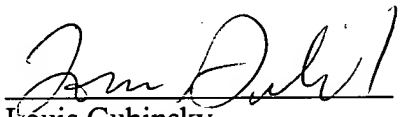
The injectable hydrogel of the present invention has specific viscoelasticity and physical properties not disclosed nor suggested by Matsuda. It is these properties in combination which provide remarkable superior aspects of the present invention allowing the practical use as an injectable. Applicants' claims are not disclosed by Matsuda and certainly are not obvious over Matsuda.

In paragraph 9 of the Office Action, claims 19 and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Matsuda. Since Matsuda does not disclose the injectable amorphous, i.e. indefinite shape, gel of the present invention, it cannot be obvious from Matsuda to include it in a container. Certainly, as the Examiner recognizes, Matsuda does not disclose an injectable gel which can be in a container and then pushed out as a gel for injection. As it has been earlier discussed, the products in Example 27 of Matsuda are not hydrogel as defined in the present invention, but are in the form of a film. Even when such a film is immersed in sterilized water, it remains as a definite film shape and as such, does not have the amorphousness of the hydrogel of the present invention enabling it to be pushed out of a container. Once the Examiner determines Applicants' hydrogel and the process for preparing hydrogel claims are patentable, certainly, then Applicants' claims 19, 20 and 21 are also patentable.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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